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**Health and Environmental Effects
Profile for Quinoline**

**(U.S.) Environmental Protection Agency
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16. ABSTRACT The Health and Environmental Effects Profile for <u>quinoline</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Quinoline</u> has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for <u>quinoline</u> is $12.48 (mg/kg/day)^{-1}$ for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.		
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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR QUINOLINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA and CERCLA dockets.

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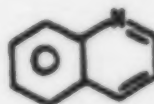
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstracts Service
CS	Composite score
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EC ₅₀	Median effective concentration
2-FAA	N-2 fluorenylacetamide
GI	Gastrointestinal
IGC ₅₀	Concentration inhibiting 50% growth
i.p.	Intraperitoneal
i.v.	Intravenous
K _{oc}	Soil adsorption constant
K _{ow}	Octanol-water partition coefficient
LC ₅₀	Concentration lethal to 50% of recipients
LD ₅₀	Dose lethal to 50% of recipients
MED	Minimum effective concentration
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per thousand
RNA	Ribonucleic acid
RQ	Reportable quantity
SGOT	Serum glutamic oxaloacetic transaminase
s.c.	Subcutaneous
TPA	Tetradecanoyl phorbol acetate

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Quinoline is also known as benzo[b]pyridine, i-benzazine, chinoleine and leucoline (Windholz, 1983). The structure and empirical formula for quinoline are given below:



Empirical formula: C_9H_7N

Molecular weight: 129.16

The CAS Registry number of quinoline is 91-22-5.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Quinoline is a colorless, hygroscopic liquid that darkens with age. It has a pungent odor and is soluble in water, alcohol, ether, benzene and carbon disulfide (Hawley, 1981). Quinoline is sparingly soluble in water and more easily soluble in hot water (Windholz, 1983). Selected physical properties are as follows (Holter, 1982; Weast, 1984; Verscheueren, 1983, unless otherwise noted):

Melting point:	-15°C
Boiling point (760 mmHg):	237.63°C
Refractive index:	1.62928
Density at 30°C:	1.08579 g/cm ³
Vapor pressure at 59.7°C:	1 mm Hg
at 103.8°C:	10 mm Hg
at 25°C:	9.10×10^{-3} mm Hg (Smith et al., 1978)
Henry's law constant:	2.49×10^{-7} atm-m ³ /mol ⁻¹ (calculated by the method of Neely and MacKay, 1982)
Water solubility at 25°C:	6110 mg/L (Smith et al., 1978)

Log K_{ow}:

2.03

Quinoline is a weak tertiary base ($K_b = 8.9 \times 10^{-10}$), which forms salts with acids. It exhibits reactions common to benzene and pyridine. Both electrophilic and nucleophilic substitution reactions are possible with quinoline. The benzene ring of quinoline is oxidized to quinolinic acid by strong oxidizing agents (Holter, 1982).

1.3. PRODUCTION DATA

Quinoline is produced synthetically by several routes. The best known process is the Skraup reaction. In this process quinoline is produced by the reaction of aniline, nitrobenzene and glycol with sulfuric acid and an oxidizing agent. It can also be manufactured from coal tar. When manufactured from coal tar, quinoline is distilled from the lower boiling tar oil bases. Typical product composition from this method is 92 wt % quinoline, 5 wt % isoquinoline and 3 wt % other impurities (Holter, 1982). Manufacturers of quinoline are Eastman-Kodak in Rochester, NY; Fairmont Chemical Co. in Newark, NJ; EM Laboratories, Inc. in Elmsford, NY; Healey and Co. in New York, NY; and Koppers Co. in Follansbee, WV (U.S. EPA, 1985). In 1978, ~226.8 metric tons of quinoline were produced and consumed in the United States (Holter, 1982).

1.4. USE DATA

Quinoline is used mainly as an intermediate in the manufacture of other products including 8-hydroxyquinoline, niacin (a vitamin) and halogenated-8-quinolinolate. Other uses are as a catalyst, a corrosion inhibitor, an analytical reagent, in metallurgical processes, in polymers and agricultural chemicals, in medicine and in dyes (Holter, 1982).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The ability of quinoline to undergo chemical reactions, photolysis, biodegradation and transport to air and sediment determine its aquatic fate. In aqueous solution at pH 3, 5 and 7 quinoline is protonated 98, 39 and 0.6%, respectively (Smith et al., 1978); quinoline contains no hydrolyzable groups. In environmental aquatic media, quinoline does not hydrolyze (Smith et al., 1978). The free radical oxidation by $RO_2\cdot$ has a reported half-life of 8 years (Smith et al., 1978), indicating that the fate of quinoline is not greatly affected by this reaction.

In aquatic media, quinoline is susceptible to photolysis, as indicated by the absorption spectrum in aquatic media (Smith et al., 1978). The spectral range of absorption is reported to be pH dependent, thus, a faster rate of photolysis has been reported at higher pH (Smith et al., 1978). Neely and MacKay (1982) reported that the photolysis half-life of quinoline changes throughout the year. Recorded summer vs. winter rate constant ratios for photochemical reaction of quinoline are 7.2 (Mill et al., 1981) and 6.0 (Neely and MacKay, 1982), respectively. During midsummer, the near surface half-life of quinoline in aqueous systems with natural sunlight has been reported to be 21 days (Mill et al. 1981) and 25 days (Zepp and Baughman, 1978). The study of quinoline in the presence of 9.5 $\mu\text{g/ml}$ humic acids resulted in a half-life of 5.3 days (Choudry, 1983), which indicates that humic acids may act as a photosensitizer in accelerating the photochemical reaction of quinoline in water. Mill et al. (1981) reported that the photolysis of quinoline in natural sunlight is ~4 times faster in the presence than in the absence of humic acid. The importance of aquatic photolysis as a mechanism for degrading quinoline in natural sunlight may, depend on pH, presence of humic acids, depth of water, season and latitude.

Biodegradation may be an important chemical removal process depending on the nature of the aqueous media. By one-compartment modeling, the biodegradation half-lives have been estimated to range from 0.5 hours in streams, ponds and eutrophic lakes to >400 days in oligotrophic lakes (Smith et al., 1978). In laboratory studies with natural water, >95% biodegradation occurred in 48 hours, 60 hours and 11 days for creek water, pond water and oligotrophic lake water, respectively, adaptation of the lake water greatly enhanced the degradation rate (Smith et al., 1978; Bohonos et al., 1977). The Japanese MITI test indicated little evidence of biodegradation of quinoline, since biodegradation as measured by oxygen consumption exceeded 30% after 2 weeks (Sasaki, 1978). The standard protocol for this biodegradation test is described as follows (Sasaki, 1978):

1. Proportion of test substance to active sludge is usually 100 ppm to 30 ppm
2. Test temperature $25 \pm 2^{\circ}\text{C}$
3. pH of the sludge supernatant 7.0 ± 1
4. Test period is 2 weeks
5. The percentage biodegradation from oxygen consumption is calculated as follows:

$$\text{Percentage biodegradation} = \frac{\text{BOD} - B}{\text{TOD}} \times 100$$

Where: BOD= biological oxygen demand (mg)
 B= Oxygen consumption of basal culture medium
 TOD= Theoretical oxygen demand required when substance is completely oxidized.

6. The percentage biodegradation from results of direct analysis is calculated as follows:

$$\text{Percentage biodegradation} = \frac{S_b - S_a}{S_b} \times 100$$

Sa: Residual amount of test substance or total organic carbon after completion of the test

Sb: Residual amount of compound or organic carbon in the blank test with water to which only the test substance has been added.

Chou and Bohonos (1979) reported that total biodegradation of quinoline in environmental aquatic systems occurred rapidly, in <1 day, after an initial lag time of 2 days. The biodegradation of quinoline by isolated organisms, Pseudomonas putida, also has been reported (Kucher et al., 1980). Based on rate constants for biodegradation in streams, ponds and lakes, it can be concluded that biodegradation is the primary removal process in all but oligotrophic lakes, where photolysis is the most important transformation process (Smith et al., 1978).

Volatilization is not expected to be an important transfer mechanism given the low vapor pressure and moderate water solubility of quinoline. Estimates using Henry's law constant (see Section 1.2.) and the mass transfer coefficient value given by Smith and Bomberger (1980) also predict a low volatilization from water. Similar conclusions regarding the volatility of quinoline from aqueous phase have been drawn by other authors (Neely, 1982; and Neely and Mackay, 1982). Laboratory studies (Smith et al., 1978) and the one-compartment modeling study (Neely and MacKay, 1982; Neely, 1982) indicate that absorption to sediment may not exceed 2% of the total compound and is, therefore, not an important transport process. Based on a K_{ow} of 100, a BCF of 31 has been estimated by Neely and MacKay (1982). In a static exposure study with fathead minnows, Pimephales promelas, Southworth et al. (1980) observed a BCF of 8; therefore, it is unlikely that quinoline will bioaccumulate significantly in aquatic organisms.

2.2. AIR

The absorption spectrum of quinoline in water (Smith et al., 1978) indicates that quinoline might also absorb light in air; therefore, photolysis is possible in the atmosphere. Neely (1982) reorganized photodegradation of quinoline in air is possible, however, one-compartment modeling predicted very little degradation of quinoline in the atmosphere.

Measurable amounts of quinoline were detected in suspended particulate matter in the air above New York City (Dong et al., 1977). The dry deposition of the sorbed particulates may be possible, although the importance of this process cannot be determined because of the lack of data. Although quinoline is slightly soluble in cold water removal from air by wet deposition is likely. Kawamura and Kaplan (1983) found 0.7-2.0 $\mu\text{g}/\text{L}$ quinoline and its quinoline and their substituted compounds, in Los Angeles, CA rain water, using an extraction and identification procedure having a 47.6% recovery. This amount indicates that significant amounts of quinoline may be transported from the atmosphere by wet deposition.

2.3. SOIL

Pertinent data regarding oxidation, photolysis or any other chemical reactions of quinoline in soil were not located in the available literature cited in the Appendix. Based on information available for quinoline in water, hydrolysis and oxidation are not expected to be important degradation processes. Photolysis may be possible on soil surfaces, but the importance of this reaction is not known. The microbial degradation of quinoline in soil has been reported in a few studies. Grant and Al-Majjar (1976) reported that bacteria isolated from garden soil used quinoline as the sole source of carbon during aerobic degradation. The data of Smith et al. (1978) and Neely (1982) indicate that biodegradation in soil may be significant.

Estimations based on physical properties have been made regarding the transport of quinoline in soil. Quinoline is expected to be leached from soil because of its moderate water solubility and the low $\log K_{ow}$ of 2.03 (Verschueren, 1983). The K_{oc} values of 66.1 and 302.9 calculated using the following two equations, respectively: $\log K_{oc} = 1.0 \log K_{ow} - 0.21$ (Reinbold et al., 1979, equation 2-1) and $\log K_{oc} = 1.377 + 0.544 \log K_{ow}$ (Lyman et al., 1982, equation 2-2). A K_{oc} value of 66.1 ranks quinoline as highly mobile in soil while a value of 302.9 ranks it as moderately mobile (Swann et al., 1983). The detection of quinoline in groundwater (Stuermer et al., 1982; Humenick et al., 1982) indicates that leaching may be a significant transport process. Volatilization from soil is not expected to be significant based on quinoline's low vapor pressure and moderate water solubility.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET data base reported concentrations of 15.0 $\mu\text{g/l}$ quinoline in the Yadkin-Pee Dee River Basin in Brunswick, NC, and 10 $\mu\text{g/l}$ in the Tennessee River Basin in Marshall, KY. Quinoline has been detected in wood preservative wastewater in Central Texas at a concentration of 260 mg/kg water (Adams and Giam, 1984). Quinoline has also been detected in groundwater near underground coal gasification sites in Wyoming and Texas (Stuermer et al., 1982; Humenick et al., 1982) and in the River Maas at Brakel (Meijers and Vanderleer, 1976). In addition, measurable concentrations of quinoline (ranging from nondetected to 6.6 $\mu\text{g/g}$ organic carbon) were detected in the sediments from Lake Washington and Puget Sound, WA (Furlong and Carpenter, 1982).

3.2. FOOD

Pertinent data regarding exposure to quinoline in food were not located in the available literature as cited in the Appendix.

3.3. INHALATION

Quinoline was analyzed in the air emissions from coke quench towers in Lorain, OH. Although no quantitative data were reported, a significant quantity was detected, rating quinoline as a potential health hazard (York Research Corp., 1979). Quinoline was measured in the air above shale oil wastewater in Colorado and Utah (Hawthorne and Sievers, 1984), in rainwater from Los Angeles, CA (Kawamura and Kaplan, 1984) and sorbed to particulate matter in the air above New York City in concentrations of 22 and 69 ng/1000 m^3 air (Dong et al., 1977). Quinoline has also been detected in the smoke of various cigarettes in the following concentrations: 19.67 $\mu\text{g/cigarette}$ for 85 mm nonfiltered, 0.62 $\mu\text{g/cigarette}$ for 100 mm, 55 mm

smoked filtered, and 1.2 μg /cigarette for 100 mm, 55 mm smoked nonfiltered (Dong et al., 1978).

3.4. DERMAL

Pertinent data regarding dermal exposure to quinoline were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Data from an early study of the metabolism of quinoline in rabbits suggested the minimum extent to which quinoline is absorbed from the GI tract. Smith and Williams (1955) dosed rabbits orally with quinoline at 250 mg/kg bw and collected all urine for the next 24 hours. From the 24-hour urine sample, ~0.5-1% of the dose of quinoline was recovered. Refluxing the urine with acid for 1.5 hours resulted in the liberation of quinoline (presumably from urinary metabolites) equivalent to an additional 6-11% of the dose. These data suggest that at least 6-12% of an oral dose of quinoline was absorbed from the GI tract of rabbits.

Holter (1982) reported a dermal LD₅₀ in rabbits of 540 mg/kg and stated that quinoline is absorbed rapidly through the skin.

4.2. DISTRIBUTION

Pertinent data regarding the tissue distribution of quinoline were not located in the available literature as cited in the Appendix.

4.3. METABOLISM

The metabolism of quinoline was studied in vivo in dogs and rabbits and in vitro using liver preparations from several animal species. An experiment using dogs provided data regarding both the extent and the rate of the metabolism of quinoline (Novack and Brodie, 1950). In one phase of this experiment, quinoline was injected intravenously at 25 mg/kg bw, and plasma concentrations were measured periodically during the following 4 hours. The plasma level of quinoline dropped from 16.9 µg/l at 15 minutes post-treatment to 0.7 µg/l at 4 hours, from which the authors inferred that quinoline was metabolized rapidly.

In another phase of this experiment, dogs were treated intravenously with quinoline at 20 or 25 mg/kg bw and urine was collected for the following 24 hours. Nevack and Brodie (1950) determined that excretion of quinoline and its metabolites was complete within 24 hours post-treatment. In this experiment, <0.5% of the administered dose of quinoline was recovered in the urine within 24 hours; the authors concluded that virtually the entire dose of quinoline had been metabolized. The urine was analyzed for metabolites of quinoline. The only metabolite identified was 3-hydroxyquinoline, equivalent to ~31% of the administered dose of quinoline. About 4% of this metabolite occurred in the free form and the remainder occurred in a conjugated form. Biliary or fecal excretion was not studied in this experiment.

In another in vivo study, 16 rabbits were given 8 g of quinoline orally (~0.5 g/rabbit); the urine was collected for 24 hours and fractionated into portions containing sulfate conjugate or glucuronide conjugate (Smith and Williams, 1955). The sulfate conjugate portion contained as the major metabolite 6-hydroxyquinolyl-5-sulfuric acid, which upon acid hydrolysis yielded 5,6-dihydroxyquinoline. The glucuronide conjugate fraction contained 3-hydroxyquinoline and 2,6-dihydroxyquinoline. Collectively, these metabolites accounted for a small proportion of the original dose of quinoline. In a study in guinea pigs, Cowan et al. (1978) mentioned that quinoline N-oxide is a urinary metabolite of quinoline.

The results of several in vitro metabolism studies with quinoline are summarized in Table 4-1. Clearly, oxidation (hydroxylation) predominates in the metabolism of quinoline.

Few species differences in the metabolism of quinoline were noted. Lung microsomal preparations from rabbits, but not from guinea pigs, metabolized quinoline to the N-oxide (Cowan et al., 1978).

TABLE 4-1

Metabolites of Quinoline From In Vitro Experiments

Species	Tissue Preparation	Metabolites	Reference
Rat	liver homogenate	5,6-dihydroxy-5,6-dihydroquinoline 2-hydroxyquinoline 3-hydroxyquinoline quinoline N-oxide 5,6-dihydroxy-5,6-dihydroisoquinoline	LaVoie et al., 1983
Rat	liver microsomal preparation	5,6- <u>trans</u> -dihydroxy-5,6-dihydroquinoline quinoline N-oxide 3-hydroxyquinoline	Tada et al., 1982
Rabbit	microsomal cytochrome P-450	3-hydroxyquinoline	Stubley et al., 1977
Rabbit, hamster, guinea pig, rat, mouse	liver microsomal preparations	quinoline N-oxide	Cowan et al., 1978
Rabbit	lung microsomal preparations	quinoline N-oxide	Cowan et al., 1978
Rabbit	aldehyde oxidase from hepatocellular cytosol	2-hydroxyquinoline	Stubley et al., 1977
Rabbit	enzyme preparation	2-hydroxyquinoline	Knox, 1946

Within a species, the position preferentially hydroxylated depended on the specific hepatic preparation used. For example, cytosolic preparations from rabbit liver hydroxylated quinoline at the 2-position, but rabbit hepatic microsomal preparations hydroxylated quinoline at the 3-position (Stubley et al., 1977). The former preparation was rich in aldehyde oxidase activity and the latter was greater in cytochrome P-450 mixed function oxidase activity.

Based on the in vitro and in vivo data available, the U.S. EPA (1983) proposed a metabolic scheme, presented in Figure 4-1. Germane to the demonstrated carcinogenicity and mutagenicity associated with quinoline is the proposed formation of a 3,4- or a 5,6-epoxide intermediate having the potential of binding to DNA. Tada et al. (1982) observed the binding of quinoline metabolites to DNA, RNA and polynucleotides which, upon treatment with acid or alkali, yielded 3-hydroxyquinoline, further supporting the hypothesis of a reactive epoxide intermediate.

4.4. EXCRETION

Quinoline and its metabolites appear to be excreted through the urine, although data regarding other routes of excretion were not located. Smith and Williams (1955) recovered 0.5-1.0% of an oral 250 mg/kg bw dose of quinoline in the urine of rabbits within 24 hours. Within this same period, metabolites equivalent to 6-11% of the original dose of quinoline were recovered.

Novack and Brodie (1950) determined that urinary excretion of quinoline and its metabolites in dogs was virtually complete within 24 hours of a 20-25 mg/kg bw i.v. dose. About 0.5% of the original dose of quinoline was recovered from the urine of treated dogs as parent compound. 3-Hydroxyquinoline, as free and conjugated forms, accounted for ~30% of the administered dose.

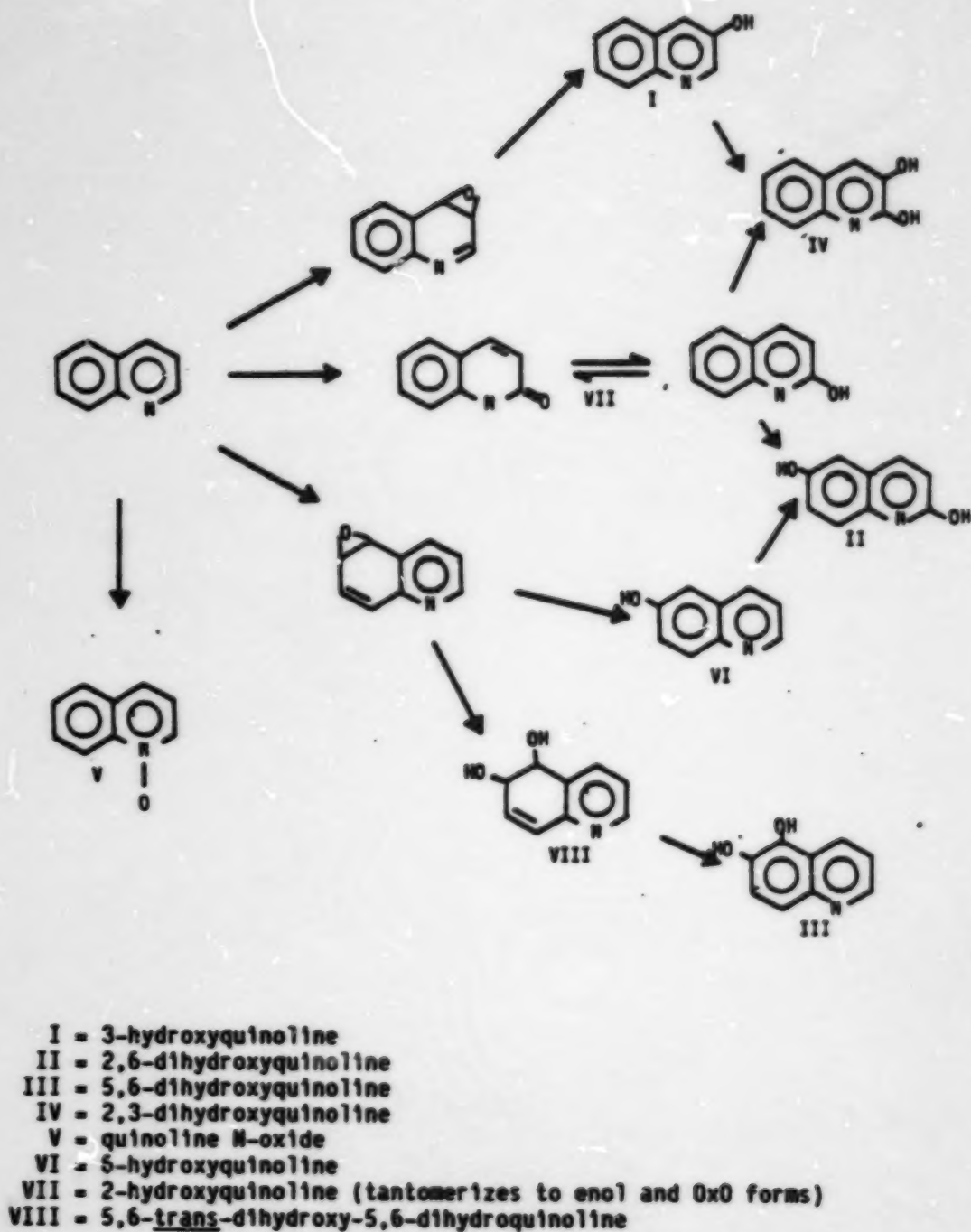


FIGURE 4-1

Proposed Metabolic Scheme for Quinoline

Source: U.S. EPA, 1983

5. EFFECTS

5.1. CARCINOGENICITY

Several experiments using laboratory animals have established the carcinogenic activity of quinoline.

In the first study groups of 20 male Sprague-Dawley rats were maintained on dietary levels of quinoline of 0.05, 0.10 and 0.25% (Hirao et al., 1976). A control group of six rats was maintained on a basal diet without added quinoline. The purity of the compound was >99.8%. Results of quinoline feeding are presented in Table 5-1. All quinoline treated groups experienced early mortality that was toxicity related. The treated groups exhibited a dose-related decrease in body weight gain. Final body weights were 677.5, 556.0, 451.0 and 330.4 g in the control, low-, middle- and high-dose groups, respectively. Food consumption was not reported. The mean survival period for the treated groups were 36.5 weeks in the low-dose, 27.3 weeks in the middle-dose and 20.0 weeks in the high-dose groups, the control rats were killed after 40 weeks. A dose-related increased incidence of hemangioendothelioma involved all treated groups but the incidence of hepatocellular carcinoma was not seemingly related to dosage level with the possibility of competing toxicity occurring in the higher doses (incidences of hepatic nodular hyperplasias followed the same pattern). Rats that died before 16 weeks of treatment were excluded from the study. Statistical analyses were not performed.

In another study hemangioendotheliomas were also produced in Sprague-Dawley rats (male only) maintained on a dietary concentration of containing 0.075% quinoline (purity not reported) for 30 weeks (Shinohara et al., 1977). A control group of 10 rats was also maintained in this Japanese study. A increased incidence (6/20) of hemangioendotheliomas occurred in

TABLE 5-1

Incidence of Tumors in Male Sprague-Dawley Rats Treated Orally
with Selected Concentration of Quinolone in the Diet

Quinolone Dietary Concentration (%)	Number of Rats Started	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Target Organ	Tumor Types observed and Tumor Incidences	
						Hepatocellular Carcinoma	Hemangioendo- thelioma
0	6	NA	40	>99.8	liver	0/6	0/6
0.05	20	36.5	36.5			3/11	6/11
0.10	20	27.3	27.3			3/16	12/16
0.25	20	20.0	20.0			0/19	18/19

QUALITY OF EVIDENCE

Strengths of Study: The compound was administered by a relevant route at three dosage levels covering a 5-fold range in dose ~7.5-37.8% of oral LD₅₀. It is not certain whether the liver vascular tumors are benign or malignant.

Weakness of Study: Only one sex of one species was studied; small numbers of animals were used, particularly in the control group; high rate of early mortality; study terminated at <40 weeks; statistical analyses were not performed. It is not sure from the reported study whether macro- and microscopic pathological examinations were performed on other major organs.

Overall Adequacy: Adequate, but marginal.

Comments: Rats that died within 16 weeks were excluded from the study.

*Source: Hirao et al., 1976

NA = Not applicable

quinoline treated rats (Table 5-2). The authors lumped benign and malignant angiomatous (vascular) liver tumors into the "hemangioendothelioma groups". Thus it indeterminates the degree of malignancy in the hemangioendothelioma group (six male rats in 20 rats). Hepatocellular carcinoma did not occur in either control or quinoline treated rats.

In another part of this experiment, 8-week-old DDY mice, Wistar rats, Syriangolden hamsters and Hartley guinea pigs were fed diets containing 0.2% quinoline (purity not reported) for up to 30 weeks. Animals that died before 26 weeks of treatment were excluded from the study. All survivors were killed for necropsy at 30 weeks. Tumors did not develop in hamsters (effective number = 25 males and 19 females, 50 at start of experiment) or guinea pigs (effective number = 21 males, 17 females, 44 at start of experiment) exposed to quinoline. Tumors developed in both rats and mice (see Table 5-2), however, control animals were not maintained in this experiment. In both of these species, the incidence of hemangioendotheliomas was higher than the incidence of hepatocellular carcinoma. On the other hand, at the early sacrifice time of 30 weeks, hamsters and guinea pigs did not show carcinogenic responses.

The development of hyperplastic liver nodules in response to test chemicals applied as initiators or promoters in rats has been used in Japan as a short-term test for chemical carcinogenesis. In one such study, quinoline was tested as a hyperplastic nodule promoting agent (Tatematsu et al., 1977). Twelve male Sprague-Dawley rats were given an i.p. injection of diethylnitrosamine (DEN) at 200 mg/kg bw as an initiating agent. A diet containing quinoline (purity not reported) at 0.25% was fed for 2 weeks beginning 2 weeks after initiation with diethylnitrosamine. A two-thirds partial hepatectomy was performed at the midpoint of the quinoline feeding

TABLE 5-2

Incidence of Tumors in Rats and Mice Treated Orally with Selected Concentration of Quinoline in the Diet

Species/Strain	Sex	Concentration (%)	Duration of Treatment (weeks)	Duration of Study (weeks)	Target Organ	Tumor Type	Tumor Incidence
Rat/Sprague-Dawley	M	0.0 0.075	MA 30	30 30	liver	hemangioendotheliomas ^a	0/10 6/20
Rat/Wistar	M F	0.2 0.2	30 30	30 30	liver	hepatocellular carcinoma	1/10 0/10
Mouse/BDY	M F	0.2 0.2	30 30	30 30		hemangioendothelioma ^b	9/10 0/10
	M F	0.2 0.2	30 30	30 30	liver	hepatocellular carcinoma	2/15 2/22
	M F	0.2 0.2	30 30	30 30		hemangioendothelioma ^b	11/15 7/22

QUALITY OF EVIDENCE

Strengths of Study: Histopathological examinations of the liver were performed; a high incidence of endotheliomas occurred in treated rats and mice; both sexes of rats and mice were used in second experiment.

Weakness of Study: Only one dosage level was used in each experiment; only one sex of animal was used in the first experiment; controls were not used in second experiment; statistical analyses were not performed; it was not clear if organs and tissues other than liver were examined histologically. Hemangioendotheliomas are lumped benign and malignant vascular liver tumors, thus not allowing delineation between the two.

Overall Adequacy: Adequate only as supportive evidence for the carcinogenicity of quinoline

Comments: In the second experiment, pneumonia reduced numbers of mice ~50%; lethality data in other species were not provided.

^aSource: Shinohara et al., 1977

MA = Not applicable

^aIncludes benign and malignant tumors

^bIt was not stated whether hemangioendotheliomas included both benign and malignant tumors.

period to enhance growth in a normally quiescent organ. A control group of 12 rats was treated with diethylnitrosamine and subjected to partial hepatectomy as were treated rats, but the controls were fed a basal diet without added quinoline. Rats were killed for histopathological examination of the liver 4 weeks after treatment with diethylnitrosamine. A statistically significant increase in the number of hyperplastic nodules (per cm² of liver slice surface area) (p-value not reported) was recorded in treated rats (P-value not reported).

In a similar type of experiment, Ito et al. (1983) fed a diet containing 0.25% quinoline (purity not reported) to a group of 14 F344 rats for 6 weeks beginning 2 weeks after initiation with diethylnitrosamine (200 mg/kg bw, i.p.). A two-thirds partial hepatectomy was performed after 1 week of the quinoline-containing diet. Control rats were initiated with diethylnitrosamine and subjected to partial hepatectomy, but were fed a diet without added quinoline. Rats were killed and examined for hyperplastic nodules 8 weeks after initiation. A statistically significant (p-value not reported) increase in the surface area of liver slices that was scored as quinoline-induced hyperplastic tissue was observed in quinoline-treated rats. Such induced hyperplasia is interpreted as quinoline induction of precancerous conditions.

Tatematsu et al. (1983) also tested the ability of quinoline to promote tumors in a group of 18 male F344 rats initiated with a diet containing 200 ppm 2-FAA for 2 weeks. A single intragastric dose of carbon tetrachloride (1 mL/kg bw) as a hepatic necrotizing agent was given after 1 week of feeding 2-FAA. Rats were returned to a basal diet for 1 week after the 2-week period of 2-FAA treatment. A diet containing 0.25% quinoline (purest grade available) was then fed for 6 weeks followed by 1 week on the basal

diet, and a partial hepatectomy was performed after 1 week of the quinoline-containing diet. A control group of 30 rats was treated with 2-FAA and carbon tetrachloride and a partial hepatectomy was performed (as were the test rats), but they were fed a basal diet instead of a diet containing added quinoline. All rats were killed and examined at the end of the 10-week experimental period. In this initiation-promotion system, neither the number nor the surface area of hyperplastic nodules was greater in treated than in control rats.

In another part of this study, quinoline was tested as an initiating agent (Tatematsu et al., 1983). A diet containing 0.25% quinoline (purest available) was fed to a group of 19 male F344 rats for 6 weeks, followed by a basal diet for 1 week. Partial hepatectomy was performed after 1 week of feeding the quinoline-containing diet. Following 6 weeks of the quinoline-containing diet and 1 week of basal diet, the rats were promoted by being fed a diet containing 200 ppm 2-FAA for 2 weeks and by the intragastric administration of carbon tetrachloride (1 mL/kg bw) in the middle of the 2-FAA feeding period. The rats were then returned to a basal diet for an additional week. Control rats (30) were treated in an identical manner except that initiation with 6 weeks of dietary quinoline was not performed. All rats were killed and examined at the end of the 10-week experimental period. Quinoline was clearly an initiator in this system, as the number of hyperplastic nodules/cm² ($p < 0.001$) and the size of the nodules ($p < 0.01$) were both increased in quinoline treated rats.

Quinoline has also been shown to be a tumor initiator in the 2-stage system in the skin of female SENCAR mice (LaVoie et al., 1984). Groups of 40 female Hfd:SENCAR BR mice at 28-35 days of age were treated every other day by dermal application of a 0.75% concentration of quinoline in acetone

for a total of 10 applications. This initiation procedure resulted in the application of a total of 7.5 mg quinoline. Promotion with twice weekly applications of TPA (2.0 µg in 0.1 ml acetone) for 18 weeks was begun 10 days after the last application of quinoline. Control mice were treated in a like manner except that acetone without quinoline was applied during the promotion stage. Skin tumors developed in 53% ($p < 0.01$) of the quinoline-treated mice compared with 7.5% in acetone-tested controls.

5.2. MUTAGENICITY

Numerous reports are available regarding the mutagenicity of quinoline in both the reverse and forward mutation assays with several strains of Salmonella typhimurium. These experiments are summarized in Table 5-3. Generally, quinoline was strongly positive in S. typhimurium TA100 (Hollstein et al., 1978; Hollstein, 1977; Hashimoto et al., 1979; Talcott et al., 1976; Yoshikawa et al., 1982; Ishidate and Yoshikawa, 1980; Haworth et al., 1983; Matsumoto et al., 1978; Okamoto et al., 1979; Nagao et al., 1977). Results in strain TA98 ranged from positive (Epler et al., 1977; Yoshikawa et al., 1982; Ishidate and Yoshikawa, 1980; Haworth et al., 1983; Matsumoto et al., 1978; Okamoto et al., 1979; Nagao et al., 1977) to negative (Hollstein et al., 1978; Hollstein, 1977; Talcott et al., 1976; Hashimoto et al., 1979). In most cases strain TA100 yielded the more strongly positive result. Strains TA1537 and TA1538 yielded consistently negative results, with the exception of one assay in which quinoline was positive in TA1537 when activated by postmitochondrial supernatant from Aroclor-treated rats (Seixas et al., 1982). These results suggest that base-pair substitutions are the type of lesions induced by quinoline.

A common finding in these reverse mutation assays with S. typhimurium is that activation with S-9 from Aroclor, 3-methylcholanthrene or

TABLE 5-3
Mutagenicity of Quinoline

Assay	Indicator/ Organism	Purity/Solvent	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	<u>S. Typhimurium</u> TA98 TA100 TA1535 TA1537	commercially available product dis- solved in DMSO	plate incorporation	10, 100 and 1000 µg/plate	±S-9	±	Positive only in TA100, only with S-9 prepared from rats pretreated with Aroclor 1254, 3-methylcholanthrene or β-naphthoflavone (group 1: cytochrome p-448 inducers) but not pretreated with pheno- barbital (group 2: cyto- chrome p-450 inducers). Positive in TA100 with S-9 from human liver	Hollstein et al., 1978; Hollstein, 1977
Reverse mutation	<u>S. Typhimurium</u> TA98 TA100	commercial grade/HR	plate incorporation	500 µg/plate	±S-9	±	Positive in both strains with S-9 prepared from polychlorinated biphenyl treated rats	Hashimoto et al., 1979
Reverse mutation	<u>S. Typhimurium</u> TA98 TA100 TA1535 TA1537	twice redi- stilled, dis- solved in DMSO	plate incorporation	20, 100, 1000 µg/plate	±S-9	±	Positive in TA100, mar- ginally positive in TA98 with Aroclor-induced rat S-9 liver preparation	Talcott et al., 1976
Reverse mutation	<u>S. Typhimurium</u> TA98 TA100 TA1535 TA1537	"highest available" dissolved in DMSO	plate incorporation	1-200 µg/plate	±S-9 from livers of rats treated with Aroclor 1254 or phenobarbital	±	Positive only in TA98 and TA1537 only with S-9 from Aroclor- induced rats; margin- ally positive in TA100 with S-9	Epler et al., 1977
Reverse mutation	<u>S. Typhimurium</u> TA98 TA100 TA1537	HR, dissolved in DMSO	plate incorporation	1-2000 µg/plate	±S-9 from livers of rats treated with polychlorinated biphenyls or pheno- barbital	±	Positive in TA98 and TA100 only with poly- chlorinated biphenyl- induced S-9, S-9 from Sprague-Dawley and Fischer rats gave stronger positive re- sponse than S-9 from Donryu or Wistar rats	Yoshikawa et al., 1982; Ishidate and Yoshikawa, 1980

TABLE S-3 (cont.)

Assay	Indicator/ Organism	Purity/Solvent	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	<u>S. typhimurium</u> TA1537	MR, dissolved in DMSO	plate incorporation	200 μ M	postmitochondrial supernatant from Aroclor or pheno- barbital-treated rats	$\pm$	Positive only with postmitochondrial supernatant from Aroclor-treated rats	Seixas et al., 1982
Reverse mutation	<u>S. typhimurium</u> TA98 TA100 TA1535 TA1537	practical 96-90%, dis- solved in DMSO	plate incorporation	0-1000 μ g/plate	S-9	$\pm$	Strongly positive in TA100, TA98; marginally positive in TA1535, TA1537; positive only with activation (S-9 from Aroclor-induced rats and hamsters)	Maworth et al., 1983
Reverse mutation	<u>S. typhimurium</u> TA98 TA100	"purest grade available" in DMSO	plate incorporation	0-200 μ g/plate	S-9 from polychlo- rinated biphenyl- treated rats	$\pm$	Positive in both TA98 and TA100 with S-9 from polychlorinated bi- phenyl-treated rats	Matsumoto et al., 1978
Reverse mutation	<u>S. typhimurium</u> TA98 TA100	"purest grade available" in DMSO	plate incorporation	100 μ g/plate	S-9 from polychlo- rinated biphenyl- induced rats	$\pm$	Weakly positive in TA98, strongly positive in TA100 with activation	Okamoto et al., 1979
Reverse mutation	<u>S. typhimurium</u> strain(s) MR	MR/MR	MR	MR	rat liver super- natant	$\pm$	MC	Benson and Kubrick, 1979
Reverse mutation	<u>S. typhimurium</u> strain(s) MR	MR/MR	MR	MR	S-9 prepared from Aroclor 1254-induced ferrets	+	Aroclor 1254-induced S-9 fraction from ferrets activates quinoline similarly to S-9 from Aroclor 1254-treated rats.	Babish et al., 1981
Reverse mutation	<u>S. typhimurium</u> TA98 TA100	"purest grade available" dissolved in DMSO	plate incorporation	0-7 μ M (0-304 μ g)/ plate	S-9 from liver of rats treated with polychlorinated biphenyl	$\pm$	Positive in both TA98 and TA100	Nagao et al., 1977
Reverse mutation	<u>S. typhimurium</u> TA98 TA100 TA1535 TA1537	>97%, dissolved in ethanol	spot test	3 μ M (307 μ g)/plate	S-9 from Aroclor- induced rats	-	Preliminary screening test	Florin et al., 1980

TABLE 5-3 (cont.)

Assay	Indicator/ Organism	Purity/Solvent	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	<u>S. typhimurium</u> TA98 TA100	>97%, dissolved in ethanol	plate incorporation	0.01-15 μ M (1.3 - 1937 μ g)/plate	+S-9 from Aroclor- induced rats	-	Negative without pre- incubation, "very toxic" at concentrations >1 μ M (129 μ g)/plate	Florin et al., 1980
Forward mutation	<u>S. typhimurium</u> TA97	reagent grade dissolved in DMSO	plate incorporation	80 μ M (10.3 μ g)/ plate	postmitochondrial supernatant from Aroclor-treated rats	+	Compound had 10% of the mutagenic activity of benzo(a)pyrene, the positive control	Kaden et al., 1979
Forward mutation	<u>S. typhimurium</u> TA97	HR dissolved in DMSO	plate incorporation	260 mM	postmitochondrial supernatant from Aroclor- or phenobar- bital-treated rats	±	Positive only with post- mitochondrial super- natant from Aroclor- treated rats	Selvas et al., 1982

HR - Not reported
MC - No comment

B-naphthoflavone-treated rats was required for a positive result. These chemicals are designated Group I inducers and result in induction of enzyme systems associated with cytochrome P-448. Group II inducers such as phenobarbital induce cytochrome P-450 associated enzymes and were not successful in obtaining a positive result in these assays.

The work of Florin et al. (1980) is unique in this series of S. typhimurium reverse mutation experiments in that negative results were obtained in both a spot test and a plate incorporation test. The authors offered no explanation for this inconsistency with the existing data; however, these experiments are the only ones, where data were available, in which ethanol rather than DMSO was used as a solvent for quinoline.

Positive results were also obtained with S. typhimurium strain M677 in two forward mutation assays (Kaden et al., 1979; Seixas et al., 1982). Activation with postmitochondrial supernatant from Aroclor- but not from phenobarbital- induced rats was needed to obtain a positive result.

Other genotoxicity tests with quinoline are summarized in Table 5-4. Chromosomal aberration tests, SCE and Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyltransferase tests using cell lines derived from the Chinese hamster all required activation to yield a positive result (Matsuoka et al., 1979; Ishidate and Odashima, 1977; Ishidate and Yoshikawa, 1980; Abe and Sasaki, 1977; Bloom et al., 1982; SanSebastien and Hsie, 1982). A positive response without S-9 activation was recorded in a DNA cell-binding assay with Ehrlich ascites cells on Escherichia coli Q13 (Kubinski et al., 1981) and in an RNA and DNA-polynucleotide-binding assay in a subcellular system (Tada et al., 1980). Activation with S-9 enhanced the subcellular binding of quinoline with nucleic acids and polynucleotides. Positive results were also noted in an alkaline elution/rat hepatocyte assay without activation (Sina et al., 1983).

TABLE 5-4
Genotoxicity of Quinolone

Assay	Indicator/ Organism	Purity/ Solvent	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Chromosomal aberration	Chinese hamster lung cells	NR/NR	cell culture	0.075, 0.15 and 0.3 mg/ml	±S-9	±	Clearly positive only at highest concentra- tion; S-9 inducing agent not described.	Matsuoka et al., 1979
Chromosomal aberration	Chinese hamster lung fibroblasts	NR, in ethanol	cell culture	0.25 mg/ml	none	-	MC	Ishidate and Odashima, 1977; Ishidate and Yoshikawa, 1980
Chromosomal aberration	Chinese hamster cells	NR, in Hanks' balanced salt solution	cell culture	10^{-6} - 10^{-8} M	none	-	MC	Abe and Sasaki, 1977
Chromosomal aberration	Chinese hamster ovary cells	NR/NR	cell culture	NR	±S-9	±	S-9 inducing agent not described	Bloom et al., 1982
SCE	Chinese hamster cells	NR, in Hanks' balanced salt solution	cell culture	10^{-6} - 10^{-8} M	none	-	MC	Abe and Sasaki, 1977
SCE	Chinese hamster ovary cells	NR/NR	cell culture	NR	±S-9	±	S-9 inducing agent not described	Bloom et al., 1982
Chinese hamster ovary cell/hypox- anthine - guanine phosphoribosyl transferase assay	Chinese hamster ovary cells	NR/NR	cell culture	NR	±S-9	±	S-9 inducing agent not described	San Sebastian and Hsieh, 1982
DNA cell-binding	Ehrlich ascites cells or E. coli Q13	"highest purity avail- able"/NR	liquid incubation	30 and 300 µM	±S-9	+	Enhanced by liver extract	Kubinski et al., 1981
DNA binding assay	yeast RNA	NR/NR	liquid incubation	0.5 µM	±S-9	+	Activation produces strong positive response; group I inducing agents more effective than Group II inducing agents	Tada et al., 1980

TABLE 5-4 (cont.)

Assay	Indicator/ Organism	Purity/ Solvent	Application	Concentration or Dose	Activating System	Response	Comment	Reference
DNA-polynucleotide binding assay	calf thymus DNA, several synthetic polynucleotides	NR/NR	liquid incubation	0.5 mM	±5-9	+	Activation produces a stronger positive response	Tada et al., 1980
Alkaline elution/ rat hepatocyte assay	rat hepatocytes	NR/NR	plate incubation	0.03, 0.3 and 1.0 mM	none	+	Positive only at highest concentration	Sina et al., 1983

NR - Not reported; NC - no comment

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity or fetotoxicity of quinoline in mammals were not located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of quinoline were not located in the available literature as cited in the Appendix.

5.5. CHRONIC TOXICITY

Data regarding chronic toxicity were generated in a 40-week carcinogenicity study in male Sprague-Dawley rats (see Section 5.1.) (Hirao et al., 1976). In this experiment, groups of 20 rats were fed diets containing 0.05, 0.1 or 0.25% quinoline. A control group consisted of six rats fed a basal diet without added quinoline. The compound was at >99.8% pure. All treated groups of rats experienced early deaths, from to the toxicity of quinoline and intraperitoneal hemorrhage resulting from the rupture of vascular tumors in the liver. In addition, a dose-related decrease in final body weights and an increase in relative liver weights were recorded in all treated groups. Histologically, a dose-related increase in fatty liver changes and nodular hyperplasia were observed that paralleled the incidence trends of hepatocellular carcinoma. Hematological and clinical chemistry parameters were measured in low-dose rats. There were no treatment-related effects on hematological parameters; SGOT and serum alkaline phosphatase were elevated only slightly. Statistical analysis of the data was not performed.

Minimal toxicity data are available from the carcinogenicity study by Shinohara et al. (1977) in which a dietary level of 0.075% quinoline for 30 weeks was associated with hemangioendotheliomas in male Sprague-Dawley rats.

Upon histopathological examination, severe nodular hyperplasia, megalocytosis, fatty degeneration and increased relative weight of the liver were noted. A moderate incidence of bile duct proliferation and oval cell formation was also observed. These changes were not observed in controls. No effects on hematology or clinical chemistries were noted. In the second part of this study, male and female rats, mice, hamsters and guinea pigs were fed diets containing 0.2% quinoline for 30 weeks. Survivors were killed for examination at 30 weeks. Nodular hyperplasia, bile duct proliferation and fatty liver changes occurred in treated rats and mice, but not in treated hamsters or guinea pigs. Treated rats, mice and hamsters also developed megalocytosis and oval cell formation. The usefulness of these data, however, is compromised by the fact that control animals were not used.

5.6. OTHER RELEVANT INFORMATION

The acute toxicity of quinoline in laboratory animals has been reviewed by the U.S. EPA (1983). Pertinent data are presented in Table 5-5. Additionally, Holter (1982) stated that quinoline vapors in humans irritate the eyes, nose and throat and may cause headaches, dizziness and nausea.

TABLE 5-5
Acute Toxicity of Quinoline to Laboratory Animals*

Animal	Route of Administration	Dose	Effect
Rat	per os	331 mg/kg	LD ₅₀
Rat	inhalation	17 ppm (90 mg/m ³) for 6 hours	LC ₀
Rat	inhalation	4000 ppm (~21,000 mg/m ³) (produced by heating quinoline at 100°C) for 5.5 hours	LC ₁₀₀
Mouse	i.p.	64 mg/kg	LD _{Lo}
Rabbit	dermal	540 mg/kg	LD ₅₀
Rabbit	s.c.	200 mg/kg	LD _{Lo}
Rabbit	skin irritation test	10 mg for 24 hours	mild irritation
Rabbit	eye irritation test	250 µg	severe irritation

*Source: U.S. EPA, 1983

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Millemann et al. (1984) presented the most comprehensive summary of investigations into the toxic effects of quinoline to seven species of fish and invertebrates. In addition, the results of effects on specific taxa obtained by different researchers tend to be in good agreement with one another (Table 6-1).

Values for LC_{50} and BCF of quinoline to freshwater fish are presented in Table 6-1. Mattson et al. (1976) reported a 96-hour LC_{50} for fathead minnows, Pimephales promelas, of 46 mg/l under static nonrenewal conditions at 18-22°C. More recently, Millemann et al. (1984) reported a 96-hour LC_{50} for the same species of 0.44 mg/l at 20±1°C. Millemann et al. (1984) noted that their test protocol was identical to that of the Mattson et al. (1976) test protocol and could offer no explanation for the discrepancy between the results of these two tests. The only difference in procedure that might account for the difference in results is that the test fish were fed during the 48-hour acclimation period in the earlier study, but not in the later study.

The acute effects of quinoline on the aquatic amphibian, Xenopus laevis, was investigated by Davis et al. (1981) at three embryonic stages of development (Table 6-2). The 96-hour LC_{50} for the mid-blastula stage of 79 mg/l was ~3 times greater than that determined by Dumont et al. (1979) of 26.3 mg/l. This variation in results, although not great, may be temperature related; the Davis et al. (1981) and Dumont et al. (1979) tests were conducted at 25 and 20°C, respectively.

Millemann et al. (1984) established the 48-hour static LC_{50} values of 34.5 and 56.8 mg/l for the waterflea, Daphnia magna, and the midge larvae, Chironomus tentans, exposed to quinoline (Table 6-3). The LC_{50} value of

TABLE 6-1
Acute and Chronic Lethal Effects and Bioconcentration of Quinoline to Freshwater Fish

Species	Duration	Concentration (mg/L)	Method	Effect	Reference
Rainbow trout; embryo-larval <u>Salmo gairdneri</u>	4 days posthatch	11.0	13.3-14.2°C; flowthrough	LC50	Black et al., 1983
Rainbow trout; embryo-larval <u>S. gairdneri</u>	27 days posthatch	11.5	13.3-14.2°C; flowthrough	LC50	Millemann et al., 1984
Fathead minnow <u>Pimephales promelas</u>	96 hours	46.0	18-22°C; static	LC50	Mattson et al., 1976
Fathead minnow <u>Pimephales promelas</u>	96 hours	0.44	20±1°C; static	LC50	Millemann et al., 1984
Large mouth bass; embryo-larval <u>Micropterus salmoides</u>	7 days posthatch	7.42	20.2-23.2°C; flowthrough	LC50	Millemann et al., 1984
Large mouth bass; embryo-larval <u>M. salmoides</u>	4 days posthatch	7.5	20.2-23.2°C; flowthrough	LC50	Black et al., 1983
Fathead minnow <u>Pimephales promelas</u>	96 hours	8.0	22°C; 1°C analysts	BCF	Southworth et al., 1980

TABLE 6-2

LC₅₀ of Quinoline to Amphibian Embryos,
Xenopus laevis, Exposed under Static Conditions

Embryonic Stage	Duration (hours)	Temperature (°C)	LC ₅₀ (mg/l)	Reference
Mid-blastula	24	25	219	Davis et al., 1981
	48	25	115	
	72	25	87	
	96	25	79	
	120	25	78	
Tailbud embryo	24	25	200	Davis et al., 1981
	48	25	148	
	72	25	129	
	96	25	129	
	120	25	78	
Free swimming	24	25	135	Davis et al., 1981
	48	25	117	
	72	25	107	
	96	25	95	
	120	25	66	
Mid-blastula	96	20	26.3	Dumont et al., 1979

TABLE 6-3

LC₅₀ of Quinoline to Aquatic Invertebrates
Exposed for 48 Hours under Static Conditions

Species	Concentration (mg/L)	Temperature (°C)	Reference
Water flea <u>Daphnia magna</u>	34.5	20	Millemann et al., 1984
Widge larvae <u>Chironomus tentans</u>	56.8	23-26	Millemann et al., 1984
Widge larvae <u>C. tentans</u>	57.2	23-26	Cushman and McKamey, 1981
Snail <u>Physa gyrina</u>	183	20	Millemann et al., 1984
Amphipod <u>Gammarus minus</u>	40.9	21-24	Millemann et al., 1984

57.2 mg/l for quinoline exposure to C. tentans under similar conditions reported by Cushman and McKamey (1981) is in agreement with the results of Millemann et al. (1984). The 48-hour static LC₅₀ values of 183 and 40.9 mg/l were also established for the common Eastern North American pond snail, Physa gyrina, and the amphipod, Gammarus minus, respectively (Millemann et al. 1984) (see Table 6-3).

Schultz et al. (1978, 1980) investigated the toxic effects of quinoline to the ciliated protozoan, Tetrahymena pyriformes, over 24- and 72-hour periods. Both tests were conducted by standardized static procedures in Erlenmeyer flasks incubated at 28°C. Stationary-growth-phase cultures (3-3.5 days old, 90,000 cells/ml) were used. The 24-hour LC₁₀₀ was determined to be 799 mg/l (Schultz et al. 1978). The 72-hour IGC₅₀ was calculated to be 126 mg/l (Schultz et al., 1980).

6.2. CHRONIC EFFECTS

The LC₅₀ of quinoline to embryo-larval rainbow trout, S. gairdneri, and large mouth bass, M. salmoides, as determined by Black et al. (1983) and Millemann et al. (1984) under flowthrough conditions was in close agreement (see Table 6-1). Black et al. (1983) presented LC₅₀ values of 11.0 and 7.5 mg/l for rainbow trout and large mouth bass, respectively, for the period from fertilization through the fourth day posthatch (average hatching times in controls; rainbow trout, 23 days; large mouth bass, 3 days). Millemann et al. (1984) determined LC₅₀ values of 11.5 and 7.42 mg/l for rainbow trout and large mouth bass, respectively. The rainbow trout and large mouth bass were exposed from fertilization through days 27 and 7 posthatch, respectively.

6.3. PLANT EFFECTS

Millemann et al. (1984) investigated the toxic effects of quinoline to a green alga, Selenastrum capricornutum, and a diatom, Nitzschia palea. The EC₅₀ values of 202 and 104 mg/l quinoline were determined for the alga and diatom, respectively; endpoint was defined as the concentration of quinoline required to reduce the rate of ¹⁴C fixation to 50% of controls.

6.4. RESIDUE

Southworth et al. (1980) established the BCF of ¹⁴C-labeled quinoline in fathead minnows over a 96-hour period as 8.0. Suggesting that quinoline is not likely to bioaccumulate. Thomas et al. (1983) conducted in vivo studies in juvenile rainbow trout to determine uptake and elimination rates and compartmentalization of quinoline and its metabolites. Based on ¹⁴C uptake, uptake plateaus were observed after only 48 hours. Compartmentalization of ¹⁴C quinoline was ranked in order of decreasing total radioactivity: gall bladder > liver > kidney > eyes > gut > muscle > gills > carcass, on a per gram basis after 48-hour exposure. After a 24-hour depuration period, 64% of the total ¹⁴C was associated with the gall bladder. Biliary excretion was determined to be the major route of elimination. Analysis of the bile demonstrated that nearly all radioactivity was in the form of quinoline metabolites.

6.5. OTHER RELEVANT INFORMATION

Additional information regarding the toxic effects of quinoline to aquatic organisms was not located in the available literature cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or foods and ACGIH, NIOSH or OSHA occupational exposure limits were not located in the available literature as cited in the Appendix.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of quinoline were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Quinoline has been shown by Hirao and coworkers to have carcinogenic activity in animals. Male rats fed diets containing 0.05-0.25% quinoline for up to 40 weeks developed a dose-related increased incidence of liver hemangioendotheliomas (see Table 5-1) (Hirao et al., 1976). The hemangioendotheliomas could not be determined to be definitely benign or malignant in each case hence they were lumped together for purposes of reporting. Therefore, the degree of malignancy cannot be factored into the percent risk determination and assessment on the Hirao data set. In addition, the treatment appeared to be associated with hepatocellular carcinoma at lower doses.

Supporting evidence for vascular hepatocarcinogenicity (hemangioendotheliomas) of quinoline was provided by Shinohara et al. (1977). These investigators associated liver hemangioendotheliomas in male rats with a 30-week exposure to a diet containing 0.075% quinoline, and in male and female rats and mice with a diet containing 0.2% quinoline for 30 weeks (see Table 5-2).

These authors, also could not report actual number of animals with malignant liver vascular tumors. Neither Hirao or Shinohara examined all tissues and organs to see if the vascular tumorigenicity of quinoline was a wide spread phenomena or just localized in the liver. As such, neither of these studies should be considered comprehensive cancer bioassays. In further support of quinoline carcinogenicity, various short-term tests were performed in mice and rats (skin and liver). Quinoline at 0.25% of the diet for at least 2 weeks successfully promoted hyperplastic nodule formation in the livers of male rats later initiated with diethylnitrosamine (Tatematsu

et al., 1977; Ito et al., 1983). These nodule-formations in liver, characterized by hypercellularity, are considered to be preneoplastic growths. This dietary level of quinoline for 6 weeks did not, however, promote liver hyperplastic nodules in rats initiated with 2-FAA and carbon tetrachloride (Tatematsu et al., 1983). A diet containing 0.25% quinoline fed to rats for 6 weeks successfully initiated hyperplastic nodule formation in rats promoted with 2-FAA (Tatematsu et al., 1983).

In the 2-stage mouse skin tumor assay, quinoline applied every other day for 10 applications initiated tumor development in >50% of treated animals. Promotion was accomplished with TPA.

Numerous reports (see Table 5-3) establish the mutagenicity of quinoline in both the reverse mutation and forward mutation assay with several strains of S. typhimurium. An activating system was required and positive results generally depended upon induction with Group I inducers such as Aroclor, 3-methylcholanthrene or β -naphthoflavone, which induce cytochrome P-448 associated enzymes. In other genotoxicity tests (see Table 5-4) with Chinese hamster cells, positive results were also obtained and metabolic activation was required. Positive results were obtained in a DNA cell-binding assay and in an RNA and DNA-polynucleotide-binding assay in a sub-cellular system without metabolic activation, although activation enhanced the magnitude of the response. Pertinent data regarding the teratogenicity or reproductive effects of quinoline were not located in the available literature cited in the Appendix.

Toxicity data were provided by the carcinogenicity studies of Hirao et al. (1976) and Shinohara et al. (1977). In rats, early mortality, a dose-related decrease in weight gain, an increase in absolute and relative liver weights, an increase in hepatic oval cells bile duct proliferation and

fatty degeneration were observed in all treated groups (0.05-0.25% quinoline in the diet) (Hirao et al., 1976; Shinohara et al., 1977). Nodular hyperplasia of the liver was also associated with the lower dietary levels of 0.05 and 0.1% (Hirao et al., 1976). Similar findings were obtained in mice fed a diet containing 0.2% quinoline for 30 weeks, and hamsters had oval cell formation and megalocytosis at 0.2%; however, no lesions were found in guinea pigs (Shinohara et al., 1977). No control animals were included in the study protocol for mice, hamsters and guinea pigs. All of the above data sets indicate the qualitative determination of risk lies with the quinoline toxicity and carcinogenic activity. The carcinogenic activities in rats and mice suggest that quinoline is a possible carcinogen to man. As such, the best classification is category C (EPA 1984). The data sets are cogent enough, however, that a cancer potency determination (see below) is indicated under the assumption that quinoline is a human carcinogen. Such an assumption is considered prudent insofar as the data sets are proximate to the next higher level of classification (B₂). This cancer potency estimate can be used in those cases where quinoline is deemed a health hazard.

The study of Hirao et al. (1976) gives dose-response data for the induction of hemangioendotheliomas in rats. These tumors could not be classified to their exact degree of malignancy. Therefore, it is assumed that a significant percentage of the hemangioendotheliomas were malignant. In this study the incidence in male rats fed diets containing 0, 0.05, 0.10 and 0.25% (0, 500, 1000 and 2500 ppm) quinoline for 40, 36.5, 27.3 and 20.0 weeks, respectively, was 0/6, 6/11, 12/16 and 18/19 in the respective groups. This increased incidence of hemangioendotheliomas was observed with increased doses of quinoline as was increased loss in body weights and

increased mortalities. A cancer response model can be derived from this data set; that is, a q_1^* for humans can be estimated (Table 8-1). The transformed doses are equivalent to 0, 25, 50 and 125 mg/kg bw/day, respectively, assuming that a rat consumes a daily amount of food equal to 5% of its body weight. The food utilization and efficiencies were not reported by these authors.

The observed incidences of hemangioendotheliomas in rats were probably the result of the combination of magnitude of dose and length of time the animals were treated, rather than the magnitude of the dose alone. The length of exposure to quinoline varied inversely with dosage level, as a consequence of the early tumor-related deaths that occurred more frequently in the higher dose groups. Because the length of exposure varied in each treatment group, the transformed doses were adjusted by a factor, $(L_e/L)^3$, to correct for the influence of varied length of exposure on the incidence of tumors. From these data, a q_1^* of $12.48 \text{ (mg/kg/day)}^{-1}$ is calculated for humans using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The conversion factor used in the calculation of this q_1^* for humans from animal data was the cube root of the ratio of the animal body weight (0.35 kg) to the human body weight (70 kg). Since a correction for time-to-tumor development was made before computation of unadjusted q_1^* s, there was no need to correct by a factor of $(L/L_e)^3$.

The rats in the Hirao et al. (1976) study also developed hepatocellular carcinomas in the low dose groups but not in the high dose (2500 ppm) group.

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: Quinoline

Reference: Hirao et al., 1976

Species, Strain, Sex: rat, Sprague-Dawley, male

Body weight: 0.35 kg

Length of exposure (t_e) = 40, 36.5, 27.3 and 20.0 weeks in control, low-, middle- and high-dose groups, respectivelyLength of experiment (L_e) = 40, 36.5, 27.3 and 20.0 weeks in control, low-, middle- and high-dose groups, respectivelyLifespan of animal (L) = 104 weeks

Tumor site and type: liver, hemangioendothelioma

Route, vehicle: oral, diet

Experimental Doses or Exposures		Transformed Dose ^a (mg/kg/day)	Incidence
			No. Responding/No. Tested or Examined
0	0	0	0/6
0.05%	500 ppm	1.08	6/11
0.10%	1000 ppm	0.90	12/16
0.25%	2500 ppm	0.89	18/19

Unadjusted q_1^* from study = $2.1333 \text{ (mg/kg/day)}^{-1b}$ Human q_1^* = $12.48 \text{ (mg/kg/day)}^{-1}$ ^aA correction factor (L_e/L)² was applied because incidence of tumors is due to interaction of magnitude of dose and length of exposure.^bContains the correction factor mentioned in footnote "a."

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Experiments that provide chronic toxicity data are summarized in Table 9-1. Chronic toxicity data in rats from the cancer study by Hirao et al. (1976) indicated that in addition to a dose-related increased incidence of hemangioendothelioma, reduced final body weights, increased relative liver weights, histopathological changes in the liver (bile duct proliferation, oval cell formation, fatty degeneration and hyperplastic nodule formation) and a markedly shortened lifespan "due to the toxic effect of (this chemical) or rupture of vascular tumors of the liver" were observed in all groups of treated rats. Treatment consisted of quinoline at 0.05, 0.10 and 0.25% of the diet for 36.5 to 20.0 weeks.

Since these effects occurred in all treated groups and appeared to be related to the carcinogenic effects, it is inappropriate to estimate a MED associated with these effects (Table 9-2). It is inappropriate, therefore, to calculate a CS associated with shortened lifespans based on the data from this study.

The same pathologic liver lesions were observed in another study in which rats were fed dietary quinoline at 0.075% for 30 weeks (Shinohara et al., 1977). Although shortened lifespan was not mentioned, it had occurred in the Hirao et al. (1976) study at a lower dose. The same liver lesions were observed in rats and mice and, milder liver lesions were observed in hamsters fed a diet containing 0.2% quinoline for 30 weeks (Shinohara et al., 1977). Controls were not used in this experiment. A more severe effect, drastically reduced lifespan, had occurred at a lower dose (0.05% of diet) in the Hirao et al. (1976) experiment. It is inappropriate, therefore, to derive a CS from the data provided by either of the Shinohara et al. (1977) experiments.

TABLE 9-1
Toxicity Summary for Quinolone Administered Orally

Species/Strain	Sex	No. at Start	Purity (%)	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Rat/Sprague-Dawley	M	20	>99.8	0.05% of diet for 36.5 weeks	25	Reduced lifespan, liver lesions, liver tumors	Hirao et al., 1976
Rat/Sprague-Dawley	M	20	>99.8	0.10% of diet for 27.3 weeks	50	Reduced lifespan, liver lesions, liver tumors	Hirao et al., 1976
Rat/Sprague-Dawley	M	20	>99.8	0.25% of diet for 20.0 weeks	125	Reduced lifespan, liver lesions, tumors	Hirao et al., 1976
Rat/Sprague-Dawley	M	NR	NR	0.075% of diet for 30 weeks	37.5	Liver lesions, elevated relative liver weight, liver tumors	Shinohara et al., 1977
Rat/Mistar	M/F	25 of each sex	NR	0.2% of diet for 30 weeks	100	Liver lesions, liver tumors	Shinohara et al., 1977
Mouse/ddy	M/F	40 of each sex	NR	0.2% of diet for 30 weeks	260	Liver lesions, liver tumors	Shinohara et al., 1977
Hamsters/Syrian golden	M/F	25 of each sex	NR	0.2% of diet for 30 weeks	166	Megacytosis and oval cell formation in liver	Shinohara et al., 1977

NR = Not reported

TABLE 9-2

Quinoline

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:

Dose:

Effect:

Reference:

RV_d:

RV_e:

Composite Score:

RQ: Data are not sufficient for deriving an RQ.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Two cancer bioassays in laboratory animals are summarized in Tables 9-3 and 9-4.

Data from the bioassay of quinoline in male rats (Hirao et al., 1976) indicate that quinoline is carcinogenic in this species. A dose-related incidence of hemangioendotheliomas developed very early in rats fed diets containing 0.05-0.25% quinoline (equivalent to 25-125 mg/kg/day). Also, no dose-related incidence of hepatocellular carcinoma occurred in this experiment. In other carcinogenicity bioassays performed at this laboratory, hemangioendotheliomas were associated with a dietary level of quinoline of 0.075% in male mice and both hemangioendotheliomas and hepatocellular carcinomas were observed in male and female rats and mice on a diet containing 0.2% quinoline (Shinohara et al., 1977). Control animals were not used in the latter experiment. Neither of these Japanese studies examined all tissues, nor reported to degree of malignancy in the reported liver tumors. Mortality was higher, thereby curtailing completion of the proposed dosing regimen. Thus increased liver tumors were observed in quinoline treated animals that had low weight gains and body weights and high mortality rates.

As discussed in Section 5.1., investigators at this laboratory have also shown that quinoline acts as an initiator (Tatematsu et al., 1983) and can also act as a promoter (Tatematsu et al., 1977; Ito et al., 1983) in the development of hyperplastic nodules of the liver of rats. These liver neoplasms are considered to be a preneoplastic lesion in these species by the EPA (1984) estimates. In other tests, quinoline has been shown to be a tumor initiator in the classic 2-stage skin carcinogenesis bioassay in female SENCAR mice (LaVoie et al., 1984).

TABLE 9-3
Bioassay of Quinolone using Male Sprague-Dawley

Exposure Route	Species/Strain	Sex	Concentration (%)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Oral	rat/ Sprague-Dawley	M	0	NA	40	>99.8	diet	liver	hepatocellular carcinomas	0/6
			0.05	36.5	36.5					3/11
			0.10	27.3	27.3					3/16
			0.25	20.0	20.0					0/19
Oral	rat/ Sprague-Dawley	M	0	NA	40	>99.8	diet	liver	hemangio-endothelioma	0/6
			0.05	36.5	36.5					6/11
			0.10	27.3	27.3					12/16
			0.25	20.0	20.0					18/19

QUALITY OF EVIDENCE

Strengths of Study: The compound was administered by a relevant route at three dosage levels covering a 5-fold range in dose -7.5-37.8% of oral LD₅₀. Both macro- and microscopic pathological and clinicopathological examinations were performed on major organs.

Weakness of Study: Only one sex of one species was studied; small numbers of animals were used, particularly in the control group; high rate of early mortality; study terminated at <40; statistical analyses were not performed.

Overall Adequacy: Adequate

*Source: Hirao et al., 1976

NA = Not applicable, rats that died within 16 weeks were excluded from the study.

TABLE 9-4
Bioassay of Quinoline using Rats and Mice

Exposure Route	Species/Strain	Sex	Concentration (%)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Oral	rat/	M	0.0 0.075	NA 30	30 30	NR	diet	liver	hemangioendothelioma ^a	0/10 6/20
Oral	rat/Wistar	M F F	0.2 0.2 0.2	30 30 30	30 30 30	NR	diet	liver	hepatocellular carcinoma hemangioendothelioma ^b	1/10 0/10 8/10 8/10
Oral	mouse/BDV	M F F	0.2 0.2 0.2	30 30 30	30 30 30	NR	diet	liver	hepatocellular carcinoma hemangioendothelioma ^b	2/15 2/22 11/15 7/22

QUALITY OF EVIDENCE

Strengths of Study: Histopathological examination of the liver were performed; a high incidence of endotheliomas occurred in treated rats and mice; both sexes of r-¹s and mice were used in second experiment.

Weakness of Study: Only one dosage level was used in each experiment; only one sex of animal used in first experiment; controls were not used in second experiment; statistical analysis were not performed; it was not clear if organs and tissues other than the liver were examined histologically.

Overall Adequacy: Adequate only as supportive evidence for the carcinogenicity of quinoline

^aSource: Shinohara et al., 1977

NA = Not applicable, NR = not reported. In second experiment, pneumonia reduced numbers of mice ~50%; lethality data in other species not provided.

^bIncludes benign and malignant tumors

Does not state whether benign, malignant or both

Neither case reports nor epidemiological studies relating quinoline to cancer in humans were located in the available literature cited in the Appendix. The evidence in animals, however, is sufficient to classify quinoline as a possible carcinogen to man. Applying the EPA (1984) Guidelines criteria for evaluating the overall weight of evidence of carcinogenicity to humans, quinoline is most appropriately classified as a Group C chemical.

A potency factor (F) for carcinogenicity can be derived for quinoline from the rat dose-response data for increased incidence of hemangioendothelioma, a term used by the authors to indicate benign and malignant liver tumors which were lumped together by Hirao and coworker, 1976. The data used to calculate F are presented in Table 9-5. The transformed doses were calculated from the dietary levels by assuming that a rat consumes a daily amount of food equal to 5% of its body weight. The exact amount of food consumed was not reported in this experiment. Because of differential quinoline related mortalities in the dose groups, the doses were corrected for time-to-tumor development by a factor $(L_e/L)^3$ before computation of the unadjusted $1/ED_{10}$ because the duration of the experiment differed for each group. The unadjusted $1/ED_{10}$ of $15.14 \text{ (mg/kg/day)}^{-1}$ was calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The potency factor (F) of $88.53 \text{ (mg/kg/day)}^{-1}$ was calculated from the unadjusted $1/ED_{10}$ by multiplying by the cube root of the human body weight (70 kg) to the weight of the rat (0.35 kg). Since a correction for time-to-tumor development was made before computation of $1/ED_{10}$, there was no need to correct by multiplying by $(L/L_e)^3$.

TABLE 9-5
Derivation of Potency Factor (F)
Agent: Quinoline

Reference:	Hirao et al., 1976
Exposure Route:	oral
Species:	rat
Strain:	Sprague-Dawley
Sex	male
Vehicle or Physical State:	diet
Body Weight:	0.35 ^a
Duration of Treatment (Le):	40, 36.5, 27.3 and 20.0 weeks in control, low, middle and high dose groups, respectively
Duration of Study (Le):	40, 36.5, 27.3 and 20.0 weeks in control, low, middle and high dose groups, respectively
Lifespan of Animal (L):	104 weeks
Target Organ:	liver
Tumor Type:	hemangioendothelioma
Experimental Doses/Exposure:	0, 0.05, 0.10, 0.25% (0, 25, 50 and 125 ppm)
Transformed Doses (mg/kg/day):	0, 1.08, 0.90, 0.89 ^b
Tumor Incidence:	0/6, 6/11, 12/16, 18/19
Unadjusted 1/ED ₁₀ (F Factor):	15.14 ^c
Corrected 1/ED ₁₀ (F Factor):	88.53

^aEstimated

^bTransformed dose altered by applying a factor (Le/L)^a to correct for time-to-tumor development because length of experiment differed for each group.

^cCorrection factor (Le/L)^a applied to transformed dose to correct for varied length of experiment before computation of unadjusted 1/ED₁₀.

Since the F factor falls between 10 and 100, quinoline is placed in Potency Group 2. A chemical in Potency Group 2 with an IARC classification of 2B (EPA, 1984 Catagory of C) has a MEDIUM hazard ranking according to the scheme for Reportable Quantities under CERCLA.

10. REFERENCES

- Abe, S. and M. Sasaoki. 1977. Chromosome aberrations and sister chromatid exchange in Chinese hamster cells exposed to various chemicals. *J. Natl. Canc. Inst.* 58: 1635-1641.
- Adams, J. and C.S. Glam. 1984. Polynuclear azaarenes in wood preservative wastewater. *Environ. Sci. Technol.* 18: 391-394.
- Babish, J.G., B.E. Johnson and K.A. Frederick. 1981. Xenobiotic metabolism and related toxicities in the ferret. *Teratology.* 24: 9A.
- Benson, J. and R. Kubrick. 1979. Mutagenicity of quinolines and their effect on rat lung and liver aryl hydrocarbon hydroxylase activity. *Annu. Rep. Inhalation Toxicol. Res. Inst., Lovelace Biomed. Environ. Res. Inst.* p. 391-396.
- Black, J.A., W.J. Birge, A.G. Westerman and P.C. Francis. 1983. Comparative aquatic toxicology of aromatic hydrocarbons. *Fundam. Appl. Toxicol.* 3(5): 353-358.
- Bloom A., S. Galloway, F.T. Nakamura, A. Tetervin and M. Armstrong. 1982. Comparison of results for SCE and chromosome aberrations for eleven compounds tested in two laboratories by a standardized protocol. *Environ. Mutagen.* 4: 397.

Bohonos, N., T.W. Chou and R.J. Spanggord. 1977. Some observations on biodegradation of pollutants in aquatic systems. Jap. J. Antibiot. 30(Suppl.): 275-285.

Chou, T.W. and N. Bohonos. 1979. Diauxic and cometabolic phenomena in biodegradation evaluations. In: Microbial Degradation of Pollutants in Marine Environments. p. 76-88. EPA-600/9-79-012.

Choudry, G.G. 1983. Humic substances: Part IV. Interactions with environmental chemicals (excluding sorptive interactions). Toxicol. Environ. Chem. 6: 231-257.

Cowan, D.A., A.L. Damani and J.W. Gorrod. 1978. Metabolic N-oxidation of 3-substituted pyridines: Identification of products by mass spectrometry. Biomed. Mass Spectrom. 5(9): 551-556. (Cited in U.S. EPA, 1983)

Cushman, R.M. and M.I. McKamey. 1981. A Chironomus tentans bioassay for testing synthetic fuel products and effluents, with data on acridine and quinoline. Bull. Environ. Contam. Toxicol. 26(5): 601-605.

Davis, K.R., W.T. Schultz and J.N. Dumont. 1981. Toxic and teratogenic effects of selected aromatic amines on embryos of the amphibian Xenopus laevis. Arch. Environ. Contam. Toxicol. 10(3): 371-391.

Dong, M.W., D.C. Locke and D. Hoffmann. 1977. Characterization of azarenes in basic organic portion of suspended particulate matter. Environ. Sci. Technol. 11(6): 612-618.

Dong, M., I. Schmeltz, E. LaVole and D. Hoffman. 1978. Aza-arenes in the respiratory environment: Analysis and assays for mutagenicity. Carcinogenesis. Vol. 3. Polynuclear Aromatic Hydrocarbons, P.W. Jones and R.I. Freudenthal, Ed. Raven Press, New York, NY. p. 97-108. (Cited in U.S. EPA, 1983)

Dumont, J.N., T.W. Schultz and R.D. Jones. 1979. Toxicity and teratogenicity of aromatic amines to Xenopus laevis. Bull. Environ. Contam. Toxicol. 22(1-2): 159-166.

Epler, J.L., W. Winton, T. Ho, F.W. Larimer, T.K. Rao and A.A. Hardigree. 1977. Comparative mutagenesis of quinolines. Mutat. Res. 39(3-4): 285-296.

Federal Register. 1980. Guidelines and Methodology used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45: 79347-79357.

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology. 18(3): 219-232.

Furlong, E.T. and R. Carpenter. 1982. Azaarenes in Puget Sound sediments. Geochim. Cosmochim. Acta. 46(8): 1385-1396.

Grant, D.J.W. and T.R. Al-Najjar. 1976. Degradation of quinoline by a soil bacterium. Microbiol. 15(61-62): 177-189.

Hashimoto, T., T. Negishi, T. Namba, S. Hayakawa and H. Hayatsu. 1979. Mutagenicity of quinoline derivatives and analogs -- Quinoxaline 1,4-dioxide is a potent mutagen. Chem. Pharmacol. Bull. 27(8): 1954-1956.

Haworth, S., T. Lawlor, K. Mortelmans, W. Speck and E. Zieger. 1983. Salmonella mutagenicity test results for 250 chemicals Environmental Mutagenesis. Suppl. 1: 3-142.

Hawley, G.G. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Co., New York. p. 879.

Hawthorne, S.B. and R.E. Sievers. 1984. Emission of organic air pollutants from shale oil wastewaters. Environ. Sci. Technol. 18: 483-490.

Hirao, K., Y. Shinohara, H. Tsuda, S. Fukushima, M. Takahashi and I. Nobuyuki. 1976. Carcinogenic activity of quinoline on rat liver. Cancer Res. 36(2, Pt. 1): 329-335.

Hollstein, M.C. 1977. Mutagenic properties of quinoline. 102 p. Univ. Microfilms Int., Order No. 7812604. From Diss. Abstr. Int. B. 39(2): 673.

Holstein, M., R. Talcott and E. Wei. 1978. Quinoline: Conversion to a mutagen by human and rodent liver. J. Natl. Cancer Inst. 60(2): 405-410.

Holter, S.N. 1982. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., M. Grayson, and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. Vol. 19. p. 532-548.

Humenick, M.J., L.N. Britton and C.F. Mattox. 1982. Natural restoration of ground water in UCG. In Situ. 6: 107-125.

Ishidate, M., Jr. and S. Odashima. 1977. Chromosome tests with 134 compounds on Chinese hamster cells in vitro - A screening for chemical carcinogens. Mutat. Res. 48(3-4): 337-353.

Ishidate Jr., M. and K. Yoshikawa. 1980. Chromosome aberration tests with Chinese hamster cells in vitro with and without metabolic activation. A comparative study on mutagens and carcinogens. Arch. Toxicol. Suppl. 4: 41-44.

Ito, N., H. Tsuda, R. Hasegawa and K. Imaida. 1983. Comparison of the promoting effects of various agents in induction of preneoplastic lesions in rat liver. Environ. Health Perspect. 50: 131-138.

Kaden, D.A., R.A. Hites and W.G. Thilly. 1979. Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to Salmonella typhimurium. Cancer Res. 39(10): 4152-4159.

Kawamura, K. and I.R. Kaplan. 1983. Organic compounds in the rainwater of Los Angeles. Environ. Sci. Technol. 17(8): 497-501.

Knox, E.W. 1946. The quinine-oxidizing enzyme and liver aldehyde oxidase. J. Biol. Chem. 163: 699-711. (Cited in U.S. EPA, 1983)

Kubinski, H., G.E. Gutzke and Z.O. Kubinski. 1981. DNA-Cell-Binding (DCB) assay for suspected carcinogens and mutagens. *Mutat Res.* 89: 95-136.

Kucher, R.V., A.A. Turovskii, N.V. Dzumedzel and A.G. Shevchenko. 1980. Microbiological transformation of quinoline by Pseudomonas putida bacteria. *Mikrobiol. Zh. (Kiev)*. 42(3): 284-287.

LaVoie, E.J., E.A. Adams, A. Shigematsu and D. Hoffmann. 1983. On the metabolism of quinoline and isoquinoline: Possible molecular basis for differences in biological activities. *Carcinogenesis (London)*. 4(9): 1169-1173.

LaVoie, E.J., A. Shigematsu, E.A. Adams, J. Rigotty and D. Hoffmann. 1984. Tumor-initiating activity of quinoline and methylated quinolines on the skin of SENCAR mice. *Cancer Lett. (Shannon, Irel.)*. 22(3): 269-273.

Matsumoto, T., D. Yoshida, S. Mizusaki, H. Tomita and K. Koshimizu. 1978. Structural requirements for mutagenic activities of N-heterocyclic bases in the Salmonella test system. *Agric. Biol. Chem.* 42(4): 861-864.

Matsuoka, A., M. Hayashi and M. Ishidate, Jr. 1979. Chromosomal aberration tests on 29 chemicals combined with S9 mix in vitro. *Mutat. Res.* 66(3): 277-290.

Mattson, V.R., J.W. Arthur and C.T. Walbridge. 1976. Acute toxicity of selected organic compounds to fathead minnows. ORD, U.S. EPA. 13 p. EPA-600/3-76-097.

Meijers, A.P. and R.Chr. van der Leer. 1976. The occurrence of organic micro- pollutants in the River Rhine and the River Maas in 1974. Water Res. 10: 597-604.

Mill, T., W.R. Mabey, B.Y. Lan and A. Baraze. 1981. Photolysis of polycyclic aromatic hydrocarbons in water. Chemosphere. 10: 1281-1290.

Millemann, R.E., W.J. Birge, J.A. Black, et al. 1984. Comparative acute toxicity to aquatic organisms of components of coal-derived synthetic fuels. Trans. Am. Fish. Soc. 113(1): 74-85.

Nagao, M., T. Yahagi, Y. Seino, T. Sugimura and N. Ito. 1977. Mutagenicities of quinoline and its derivatives. Mutat. Res. 42(3): 335-341.

Neely, W.B. 1982. Organizing Data for Environmental Studies. Environ. Toxicol. Contam. 1: 259-266.

Neely, W.B. and D. Mackay. 1982. Evaluative model for estimating environmental fate. In Modeling the Fate of Chemicals in the Aquatic Environment. K.L. Dickson, A.W. Maki and J. Cairns, Ed. Ann Arbor Science Publ. Ann Arbor, MI. p. 127-143. 4: 127-143.

Novack, L. and B.B. Brodie. 1950. Quinoline and its transformation products found in urine. J. Biological Chem. 187: 787-792.

Okamoto, H., S. Mizusaki, D. Yoshida and T. Matsumoto. 1979. Enhancing effect of carbohydrate pyrolysates on mutagenesis in Salmonella typhimurium. Agric. Biol. Chem. 43(7): 1433-1438.

Reinbold, K.A., J.J. Hassett, J.C. Means and W.L. Banwart. 1979. Adsorption of energy-related organic pollutants: A literature review. U.S. EPA, Athens, GA. EPA-600/3-79-086, p. 180.

San Sabastian, J.R. and A.W. Hsie. 1982. An analysis of mutagenic activity of quinolines in the Cho/Hgp^rt system. Environ. Mutagen. 4: 395.

Sasaki, S. 1978. The scientific aspects of the chemical substance control law in Japan. In: Aquatic Pollutants: Transformation and Biological Effects, O. Hutzinger, L.H. Von Letyoeld and B.C.J. Zoeteman, Ed. Pergamon Press, Oxford. p. 283-298.

Schultz, T.W., L.M. Kyte and J.N. Dumont. 1978. Structure-toxicity correlations of organic contaminants in aqueous coal-conversion effluents. Arch. Environ. Contam. Toxicol. 7(4): 457-463.

Schultz, T.W., M. Cajina-Quezada and J.N. Dumont. 1980. Structure-toxicity relationships of selected nitrogenous heterocyclic compounds. Arch. Environ. Contam. Toxicol. 9(5): 591-598.

Seixas, G.M., B.M. Andon, P.G. Hollingshead and W.G. Thilly. 1982. The aza-arenes as mutagens for Salmonella typhimurium. Mutat. Res. 102(3): 201-212.

Shinohara, Y., T. Ogiso, M. Hananouchi, K. Nakanishi, T. Yoshimura and N. Ito. 1977. Effect of various factors on the induction of liver tumors in animals by quinoline. Gann. 68: 785-796.

Sina, J.F., C.L. Bean, G.R. Dysart, V.I. Taylor and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat. Res.* 113(5): 357-391.

Smith, J.H. and D.C. Bomberger. 1980. Prediction of volatilization rates of chemicals in water. In: Hydrocarbons and Halogenated Hydrocarbons in the Aquatic Environment. Plenum Press, NY. p. 445-451.

Smith, J.H., W.R. Mabey, N. Bohonus, et al. 1978. Environmental Pathways of Selected Chemicals in Freshwater Systems. Part II. Laboratory Studies. U.S. EPA, Athens, GA. EPA-600/7-78-074.

Smith, J.N. and R.T. Williams. 1955. Studies in detoxication. 65. The metabolism of quinoline. New metabolites of quinoline, with observations on the metabolism of 3-, 5- and 6-hydroxyquinoline and 2,4-dihydroxyquinoline. *Biochem. J.* 60: 284-290.

Southworth, G.R., C.C. Keffer and J.J. Beauchamp. 1980. Potential and realized bioconcentration. A comparison of observed and predicted bioconcentration of azaarenes in the fathead minnow (Pimephales promelas). *Environ. Sci. Technol.* 14: 1529-1531.

Stubley, C., L. Subryan, J.G.P. Stell, R.H. Perrett, P.B.H. Ingle and D.W. Mathieson. 1977. The metabolism of N-heterocycles. *J. Pharm. Pharmacol.* 29(Suppl., Br. Pharm. Conf.): 77.

Stuermer, D.H., D.J. Ng and C.J. Morris. 1982. Organic contaminants in groundwater near an underground coal gasification site in Northeastern Wyoming. Environ. Sci. Technol. 16: 582-587.

Swann, R.L., D.A. Laskowski, P.T. McCall, K. Vanderkuy and H.J. Dishburger. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Res. Rev. 85: 17-28.

Tada, M., K. Takahashi, Y. Kawazoe and M. Ito. 1980. Binding of quinoline to nucleic in a subcellular microsomal system. Chem.-Biol. Interact. 29(3): 257-266.

Tada, M., K. Takahashi and Y. Kawazoe. 1982. Metabolites of quinoline, a hepatocarcinogen, in a subcellular microsomal system. Chem. Pharm. Bull. 30(10): 3834-3837.

Talcott, R., M. Hollstein and E. Wei. 1976. Mutagenicity of 8-hydroxy-quinoline and related compounds in the Salmonella typhimurium bioassay. Biochem. Pharmacol. 25(1): 1323-1328.

Tatematsu, M., T. Shirai, H. Tsuda, Y. Miyata, Y. Shinohara and M. Ito. 1977. Rapid production of hyperplastic liver nodules in rats treated with carcinogenic chemicals: A new approach for an in vivo short-term screening test for hepatocarcinogens. Gann. 68(4): 499-507.

Tatematsu, M., R. Hasegawa, K. Imaida, H. Tsuda and N. Ito. 1983. Survey of various chemicals for initiating and promoting activities in a short-term in vivo system based on generation of hyperplastic liver nodules in rats. Carcinogenesis (London). 4(4): 381-386.

Thomas, B.L., D.D. Daudle, R.M. Beeln and R.W. Hauf, Jr. 1983. Fate and biotransformation of quinoline in rainbow trout. Abstract of Poster presented 1983, SETAC. p. 35.

U.S. EPA. 1984. Guidelines for Cancer Risk Assessment. Federal Regulations. 49(227): 46294-46301.

U.S. EPA. 1983. Chemical Hazard Information Profile: Quinoline Draft Report. Prepared by Dynamac Corporation for U.S. EPA, Washington, DC.

U.S. EPA. 1985. TSCA Production File. On-line. February 1985.

Verschuere, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., New York. p. 1041.

Weast, R.C., Ed. 1984. CRC Handbook of Chemistry and Physics, 64th ed. CRC Press, Inc., Boca Raton, FL. p. D-208.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ. p. 1167.

York Research Corp. 1979. Analyzing organics in air emissions. Environ. Sci. Technol. 13(11): 1340-1342.

Yoshikawa, K., T. Nohmi, R. Miyata, et al. 1982. Differences in liver homogenates from Donryu, Fischer, Sprague-Dawley and Wistar strains of rat in the drug-metabolizing enzyme assay and the Salmonella/hepatic S9 activation test. *Mutat. Res.* 96(2-3): 167-186.

Zepp, R.G. and G.L. Baughman. 1978. Prediction of photochemical transformation of pollutants in the aquatic environment. *Aquatic Pollutants*. Pergamon Press, Oxford. p. 237-263.

APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in February, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983, 1984). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1984-1985. Cincinnati, OH. p. 116.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1985. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Office of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

In addition, FYI-OTS-0584-0135 was obtained, reviewed and found to be not useful.